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Leishmaniosis phytotherapy: Review of plants used in Iranian traditional medicine on leishmaniasis

Mahmoud Bahmani[1], Kourosh Saki[2], Behrouz Ezatpour[3], Somayeh Shahsavari[4], Zohreh Eftekhari[5], Mahyar Jelodari[6], Mahmoud Rafieian-Kopaei[7*], Reza Sepahvand[3]

[1]*Food and Beverages Safety Research Center, Urmia University of Medical Sciences, Urmia, Iran*

[2]*Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[3]*Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*

[4]*Young Researchers and Elite Club, Khorramabad Branch, Islamic Azad University, Khorramabad, Iran*

[5]*Research and Production Complex, Pasture Institute of Iran, Tehran, Iran*

[6]*Faculty of Veterinary Medicine, Urmia University, Urmia, Iran*

[7]*Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*

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ABSTRACT

Many native plants in traditional medicine have been used for the treatment of cutaneous leishmaniasis and the recent clinical trials have proven the efficacy of some of them. Researches conducted on these plants have shown that garlic, shallots, wormwood, yarrow, walnuts, thyme, henna plant, mimosa, aloe, wood betony, medlar, periwinkle, yeah, savory, black beans, *etc*. are effective on cutaneous leishmania. Synthetic agents in Iranian market have some disadvantages such as high cost and side effects and are painful in injections. Given the effectiveness of these plants, they can be a source of natural and safe compounds for the treatment of *Leishmania*. Therefore, more clinical researches should be done to determine the effectiveness and safety of these medicinal plants, their active ingredients and their possible toxic substances which can lead to the production of effective and safe drugs for leishmaniasis. It also might be an effective way to prepare herbal ointment on wound healing.

1. Introduction

Leishmaniasis is one of the six major infectious diseases in the world caused by various species of the genus *Leishmania*. Leishmaniasis is a public health problem in many tropical and subtropical countries like Iran [1]. *Leishmania* is the protozoan parasite whose family included Trypanosomatida. The disease is endemic in 81 countries. Annually, one to one and a half million new cases of the disease were reported in the world. Clinical features of leishmaniasis disease include cutaneous, mucocutaneous and visceral forms [2,3].

Cutaneous leishmaniasis (CL) is a parasitic disease spread by flies and common in many tropical and subtropical countries of the world. Probably about 12 million cases of CL in different parts of the world occur annually and 350 million people are at risk of developing the disease. Currently 88 countries in worldwide are infected with CL [4].

Several studies have shown that CL in the world is increasing. Annually, approximately 20 000 cases of leishmaniasis have been reported from different parts of the world and actual amount has estimated several times [5]. In Iran, approximately fifteen thousand people are infected with leishmaniasis. Based on existing researches, the actual incidence of leishmaniasis is four to five times of the current reports and incidence is 0.27 per thousand [6,7].

In this review study, related information was obtained from available ancient sources such as Iranian traditional books.

*Corresponding author: Prof. Mahmoud Rafieian-Kopaei, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran.
Tel: +98 381 334 6692, +98 913 1811842
Fax: +98 381 3330709
E-mail: rafieian@yahoo.com

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Accordingly, a wide spectrum of plants was found to be useful for cleansing and protecting the liver. Finally, the obtained data was compared with those reported in modern medicinal databases covering all *in vitro* and *in vivo* leishmaniasis investigations. In the present article, the literature review was performed by using scientific information database focusing on the keyword of leishmaniasis.

2. Chemical agents in the treatment of leishmaniasis

At the present time, various chemical agents are used in the treatment of CL. Among them, the compounds of antimony (pentavalent), antimalarial drugs like chloroquine, quinacrine, emetine, metronidazole and minomycline antibiotics, tetracycline and rifampin are also used.

Treatment depending on the parasite species and determination of specification is important to plan control and prevention. Antimony compounds are the first line treatment of CL. Its two compounds, meglumine antimonate (glucantime) and sodium gluconate acetic (pantocetam), are commercially available and 5-valent antimony compounds, glucantime, the most common medications are used to treat CL in Iran and other parts of the world [8–10]. These drugs have side effects, including increased liver enzymes. Glucantime is an expensive and painful injection drug and its usage in patients with kidney and liver problems is not permitted [11–13]. The use of compounds that are free of these problems and disadvantages, is necessary [14–16]. The use of medicinal plants in the historical record rises increasingly [17–24].

Medicinal plant is an effective source of pharmaceutical products in Iran [25–31]. These drugs are inexpensive and proven to have health effects [32–34]. Iran currently produces about 820 herbal drugs [35–38]. Today, clinical research and empirical studies on the subject of medicinal plants have been done in different parts of the world especially in Iran [23,39–44].

3. The role of indigenous medicinal plants in the treatment of leishmaniasis

In different cultures and different countries, indigenous medicinal plants are used to treat diseases, especially leishmaniasis. Table 1 shows native medical plants in Iran and their effects are scientifically proven to be effective on leishmaniasis.

Leishmaniasis is a broad-spectrum parasitic disease reported worldwide. Until now no effective vaccine or drug for the inhibition of parasite has been reported and no effective chemicals for eradication of carriers are provided [66–69].

Natural substances or compounds derived from plants are widely used against pathogenic microorganisms [70].

Based on Figure 1, the family of native plants which has the best effect of anti-leishmania is the Asteraceae family. Plants of this family seem to have certain medicinal properties and chemicals that have the effect of imposing anti-leishmania. Plants of this family include *Artemisia*, and marigold. The bioactive compounds of *Artemisia* species including artemisinin and artemether are effective against leishmania. Because the *Artemisia* includes most plants of this family, we tried to introduce the different species of the genus that grow in Iran. In Iran, there are several species of the genus *Artemisia*, which include Turkish, Kermani and Caspian *Artemisia*.

In addition to antihelminthic activity of *Artemisia*, frequency of biological activities such as germicidal, anti-fungal, viral wiring, antiparasitic and analgesic properties and antioxidant properties of the antibody and the dilation of blood vessels have been demonstrated [71–77].

Analysis has shown that the herb mountain *Artemisia* contains various compounds such as semen, sabinene, cineol, linalool, borneol, farnezole, esters and other compounds [71]. *Artemisia aucheri* (*A. aucheri*) has bioactive compounds such as flavonoids, santonian, coumarin compounds, bitter substances and volatile oils [78].

Siberian *Artemisia* contains bioactive substances including monoterpenes categories acid glycosides and 4-sezquitrepens derivatives of Oplonanon and germcran, derivatives bisabolene, salsolene ketones, camphor, 8,1 cineole of oxygenated monoterpene, sesquiterpene dehydroepiandrostrone, 1,8-cineole, β-thujon, thujon, alpha-dimethyl cyclopentane, carboxylic acid and camphor [79]. The combination of camphor, camphene, 1,8-cineole, alpha and beta-tojone, alpha-pinnene are components of Siberia *Artemisia*.

Pulmonary toxicity, anti-nutritional and repellent of *Artemisia* have already been demonstrated [80–82]. The main components of this plant include glycosides, santonins, coumarines, terpenoides and sterols, polyacetylene and flavonoids like quercetin and rotenoids which have antioxidant properties [83]. The composition of the essential oil of *Artemisia* is cineol and in extracts, tannins and flavonoids have an antiseptic effect [84–86].

Research has shown that the major compounds of *A. aucheri* include santonin, comphour and cineol [79,83,87,88]. Researches have proven that antiparasitic effects of santonin are based on paralysis of the parasites at low concentrations and poor stimulatory effect on the worms in high concentrations. Stimulatory or inhibitory action of santonin has been done through gabaergic and cholinergic stimulation mechanisms in the nervous system of worms [89]. In *Artemisia annua*, researches are more focused on terpene compounds that have antiparasitic activity, and less attention has been given to phenolic compounds of this plant, but recently antioxidant and anticancer effects of phenolic compounds has been discussed [90].

Active ingredients containing artemisinin (Figure 2) and artemether (Figure 3), two bioactive compounds against *Leishmania*, are two different forms of the pharmaceutical composition (topical and injectable) which are both effective drugs against *Leishmania*.

Artemisinin has good antiparasitic and antimalarial effect. Artemisinin levels in different sepsis ranges from 0.01% to 1.5%. Because of naturally low levels of this substance in the plant, extraction of it is very expensive [91]. Artemisinin has low solubility in water and fat. Therefore, it is possible to use this compound as a commercial antiparasitic agent because it has not disadvantages [92–95]. Therefore, if we seek new and effective materials, we should be able to prepare drugs without disadvantages in those of artemisinin.

The bioactive substances in the pharmacological tests on leishmania have been investigated and effective compounds to produce efficient and safe drugs for parasitic consumption have been produced.

This paper presented a brief overview of leishmaniasis and effective native medicinal plants to treat the wound caused by leishmaniasis. The effectiveness of the plants in traditional medicine in wound healing and cutaneous infection cases has been proven.

Table 1
Medicinal plants and their effects on the leishmaniasis.

The scientific name of the plant	Family name	English name	Research result
Zajuria multiflora Boiss.	Lamiaceae	Thyme	Thyme and yarrow extract had positive effects on wound healing of cutaneous leishmaniasis [45].
Lawsonia inermis	Lythraceae	Henna	
Calendula officinalis	Asteraceae	Marigold	The extraction of marigold at a concentration of 500 mg/mL killed all the parasites and in lower concentrations revealed anti-leishmania activity which was dose-dependent with LC_{50} of 17 μg/mL and 215 μg/mL, in alcoholic and water extracts, respectively [46].
Nerium oleander	Apocynaceae	Oleander	The number of promastigotes of *Leishmania* reduced compared to control group. Significant reduction on the process of the formation of scars and cutaneous nodules at the base of the tail of the mice was also observed compared with the control group [47].
Capsicum annuum	Solanaceae	Kapsa	
Amygdalus communis	Rosaceae	Almond	
Ricinus communis L.	Euphorbiaceae	Castor oil plant	
Achillea millefolium	Compositae	Yarrow	Increase in immobilization of parasites after 30 min compared to control group was observed and it was found that the effect of the extract was related to the time [48].
Artemisia absinthium	Compositae	Grand wormwood	
Juglans regia	Juglandaceae	Walnut	
Allium hirtifolium Boiss.	Alliaceae	Spring onion	Concentrations of 0.01–0.1 mg/mL of the extract inhibited the parasites growth on the third day and the highest concentration was effective in the first day [49].
Allium sativum	Alliaceae	Garlic	Garlic at the dose of 37 μg/mL in 48 h destroyed the existing promastigotes [50].
Aloe latex (*Aloe emodin*)	Aloaceae	Aloe	*Aloe emodin* had inhibitory effects on the growth of *Leishmania* promastigotes with LC_{50} of 52.8 μg/mL. Also, flow-cytometry results showed that it was able to induce apoptosis [51].
Arnebia euchroma	Boraginaceae	Royle	All tested concentrations (0.78, 1.5, 3.2, 6.5 and 12.5) reduced the number of leishmania parasites time dependently [52].
Artemisia annua	Asteraceae	Sweet wormwood	The concentrations of 10–100 μg/mL were effective against promastigote of *L. major* [53].
		Artemisinin	The inhibitory concentration (IC_{50}) was 25 mg/L. The extract also caused DNA fragmentation on promastigotes of *L. major* [54].
A. aucheri Bioss.	Asteraceae	Wormwood	The LC_{50} of the *A. aucheri* and *Artemisia asafetida* extracts were 4.7 and 7.5, respectively [55].
Berberis vulgaris	Berberidaceae	European berberry	A concentration of 20% reduced the mean diameter of the lesions and the complete healing was observed in 27.7% in mice [56].
Cassia fistula	Leguminosa	Amaltas	Significant improvement was observed in the length of patients lesions in both *Cassia* and glucantim groups. In both groups, the side effects such as itching and erythema were observed in 9 patients, and in this respect there was no difference between the two groups [57].
Echinacea purpura	Asteraceae	Purple coneflower	A significant improvement was seen compared to the control group [58].
Eucalyptus globulus	Myrtaceae	Blue gum	*Eucalyptus* extract and tarragon extract caused complete healing of small wounds, complete removal of the lesions and Leishman bodies and prevented the expansion of large ulcers by reducing the number of parasites [59].
Artemisia dracunculus	Compositae	Tarragon	
Mimosa tenuiflora	Fabaceae	Jurema	Extract of *Mimosa* at concentrations of 500 and 1 000 μg/L rapidly reduces parasite proliferation [60].
Peganum harmala	Zygophyllaceae	Harmal	*Peganum harmala* plus *Alkana* were effective on *L. major* in *in vitro* situation and had inhibitory effect on promastigotes [61].
Alkanna tinctoria	Boraginaceae		
Satureia hortensis	Labiatae	Winter savory	After 24 h, *Satureia* and *Nigella* extracts, in 8 percent concentration, significantly reduced the number of parasites in comparison to control group [62].
Nigella sativa	Ranunculaceae	Blach seed	
Scrophularia striata	Scrophulariaceae	Snapdragon	A concentration of 10 mg/mL control drug and a concentration of 25 mg/mL extract, on the third day, respectively caused complete elimination of *L. major* amastigotes within macrophages. Percentage of infected macrophages with increasing concentrations of the extract decreased and on the second and third days, the infected macrophages were not observed in the culture media [63].
Stachys lavandulifolia	Lamiaceae	Wood betony	The number of *Leishmania* promastigotes decreased dose-dependently with increasing concentrations of wood betony extract. Based on the results, there was not significant difference in the number of promastigotes in two concentration of Dutch medlar extract [64].
Mespilus germanica	Rosaceae	Dutch medlar	
Vinca major	Apocynaceae	Periwinkle	Purified extract of the plant *Vinca* caused significant reduction in the number of *L. major* promastigotes. Additionally, a purified extract of *Vinca* in the chloroform phase by injection form, prevented the development of ulcers caused by *L. major* in Balb/C mice compared to the untreated controls [65].

L. major: *Leishmania major*.

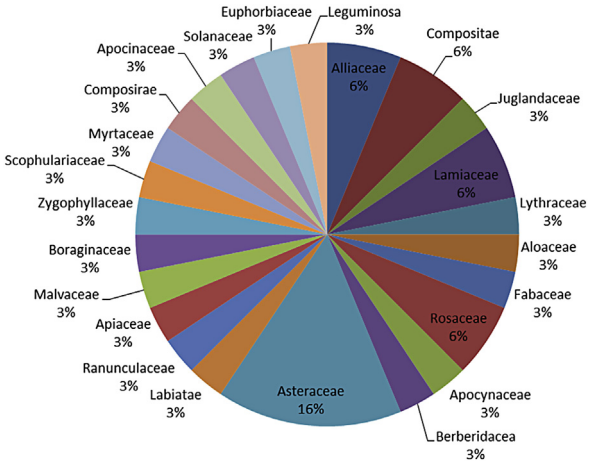

Figure 1. The native plants with good effects on leishmaniasis.

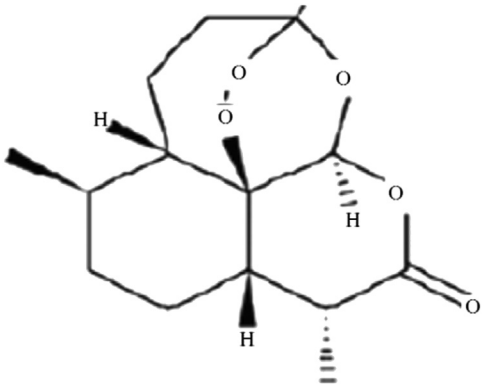

Figure 2. Artemisinin.

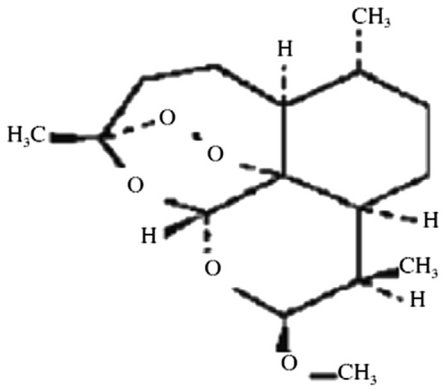

Figure 3. Artemether.

Given the well documented effects, medicinal plants can be used as herbal supplements and even alone in the treatment of leishmaniasis.

Therefore, studies on plants and their active components are suggested. If the efficiency of plants and their active ingredients are proven by rigorous scientific studies, preparation of natural medicines due to the availability of raw materials will be much more effective and less expensive than buying imported chemical drugs.

Recent studies have proven their effects, not only on leishmaniasis, but also on other diseases such as Alzheimer [96–98], diabetes [99–102], atherosclerosis [103–106], cardiovascular diseases [107–110], cancer [111,112], wound healing [111,113] and other complication [114–117]. They also can be used in the treatment of or prevention from toxicities from other substances [101,118–127]. Therefore, they might be a reliable source for preparation of new drugs.

Another important issue is the safety of natural remedies. Although natural immune therapy in different generations has been tested and approved, it is necessary to prove the overall pharmacological safety of the exact.

Chemical agents in Iranian market have disadvantages such as high cost, painful injections and side effects. Given the effectiveness of these plants, they can be a source of natural and safe agents for the treatment of *Leishmania*. Therefore, more clinical researches to determine the effectiveness and safety of medicinal plants and their active ingredients and possible toxic substances can lead to the production of efficient and safe drugs for leishmaniasis. Preparation of herbal ointment on wound healing is also an effective way of reducing injection pain and the treatment cost.

Conflict of interest statement

We declare that we have no conflict of interest.

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